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PP and 13 in Leads Section

studies (Ito et al., 2007; NYDOH, 2006; Peel et al., 2005; Tolbert et al., 2007) also reported NO₂ effect estimates using multi-pollutant models, as discussed above (section II.B.1.a). In the study by Ito et al. (2007), risk estimates were robust and remained statistically significant in multi-pollutant models that included PM_{2.5}, O₃, CO, and SO₂. NO₂ associations in Ito et al., 2007 were significant in the warm season, but not in the cool season. In two of the other 3 studies (NYDOH, 2006; Peel et al., 2005; Tolbert et al., 2007), NO₂ effect estimates generally remained positive but were often not statistically significant in multi-pollutant models.² In Peel et al., 2005, there were no significant findings in multi-pollutant models. In Tolbert et al., 2007 and NYDOH, 2006, ozone relative risks were consistently larger and significant in multi-pollutant models, in comparison to NO₂ risks.³ Two additional studies which evaluated only single pollutant models (Linn et al., 2000; Ostro et al., 2001) reported positive and statistically significant NO₂ effect estimates in locations with appreciably higher area-wide 1-hour daily maximum NO₂ concentrations (i.e., around 200 ppb). One additional multi-pollutant study (Friedman et al., 2001), examined pollution associations with the decline in asthma emergency care visits which occurred during the 1996 Atlanta Olympics, and found that reductions in ozone but not NO₂ were associated with reductions in emergency room visits.

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² As discussed above in section II.B.1, the conclusion from the ISA that NO₂ effect estimates generally remain robust in multi-pollutant models is based on evaluation of the broader body of epidemiologic evidence which includes, but is not limited to, these U.S. studies (e.g., see Figures 1 and 2 above and ISA, Figures 3.1-7, 3.1-10, and 3.1-11).

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³ The NYDOH, 2006 study stated: "The results suggest that the criteria pollutants PM_{2.5}, SO₂, O₃ and NO₂ had a statistically detectable impact on acute asthma ED visits in a community with a relatively high baseline rate of acute asthma exacerbations. In two-pollutant and three-pollutant regression models, O₃ and SO₂, and to a lesser extent maximum one-hour PM_{2.5}, were the most robust pollutants. In other words, these pollutants exhibited less change in their effect estimates as additional pollutants were added to the models. Robust effects of O₃ have been seen in previous ED asthma studies (Stjeb et al., 1996; Martins et al., 2002) and in hospital admissions studies of asthma and other respiratory diseases (Burnett et al., 1997)."

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additional study of non-specific responsiveness and removed an allergen responsiveness study that was included in the original⁷. While the additional analysis does not include new results at lower concentrations (100-250 ppb), we interpreted the results with a greater focus on 100 ppb due, in part, to the greater body of evidence available, including new epidemiological evidence (see ISA, section 3.1.3.2 for more discussion). Therefore, it also reported results specifically for an additional NO₂ exposure concentration, of 100 ppb. As with the original analysis by Folinsbee (1992), the updated meta-analysis reported that –a larger percentage of resting asthmatics, as opposed to exercising asthmatics, experienced an NO₂-related increase in airway responsiveness. The updated analysis reported that, when exposed at rest, 66% (33 of 50) of asthmatics experienced an increase in airway responsiveness following exposure to 100 ppb NO₂, 67% (47 of 70) of asthmatics experienced an increase in airway responsiveness following exposure to NO₂ concentrations from 100 to 150 ppb, 75% (38 of 51) of asthmatics experienced an increase in airway responsiveness following exposure to NO₂ concentrations from 200 to 300 ppb, and 73% (24 of 33) of asthmatics experienced an increase in airway responsiveness following exposure to NO₂ concentrations above 300 ppb. The fraction of resting asthmatics experiencing an increase in airway responsiveness was statistically significant at each of these NO₂ concentrations.

Based on this evidence, we have identified exposure to NO₂ at a level of 100 ppb to be the lowest level at which effects have been observed in controlled human exposure studies, noting that it is also the lowest level tested in the studies used in the meta-analysis. There is no evidence from this meta-analysis, however, of a threshold below which NO₂-related effects do not occur.

⁷ The updated meta-analysis added a study that evaluated non-specific airway responsiveness following exposure to 260 ppb NO₂ and removed a study that evaluated allergen-induced airway responsiveness following exposure to 100 ppb NO₂.